All information regarding future IHI Call topics is indicative and subject to change. Final information about future IHI Calls will be communicated after approval by the IHI Governing Board.

Topic 6: Sustainable circular development and manufacturing of healthcare products and their quantitative environmental impact assessment

Expected impacts to be achieved by this topic

This project will pave the way for European healthcare industries to collaborate cross-sectorially to improve the manufacturing efficiency of drug substances of chemical/biological origin (covering all chemical drug substances, proteins, oligonucleotides, vaccines or polypeptides etc.) by saving natural resources like water and fossil or fossil-based raw materials and consumables, in addition to reducing waste in accordance with circularity principles (reduce, reuse, refine, recycle).

Healthcare industries in the Organization for Economic Cooperation and Development (OECD) countries are responsible for 3-8% of natural carbon dioxide emissions[1]. The invention of new and creative technology in the field of chemistry and biotechnology will make Europe the central driver of innovation for the supply of drugs made of renewable resources. The ultimate goal of the project is to significantly reduce the environmental impact of the manufacture of medicines.

Based on life cycle assessment, most of the environmental impact of a typical medicine is generated during manufacturing operations. This project will address gradual changes in the reduction of virgin resource consumption, greenhouse gas emissions (GHG), waste generation and water consumption and minimise contaminating effluents from industry. This would be achieved by the development/introduction of shorter manufacturing routes, lower energy processes, reductions in solvent and chemical use, the introduction of biorenewable materials, and the replacement of substances of concern (e.g. PFAS = poly- and perfluorinated alkyl substances, chlorinated organic solvents) with more benign alternatives (which may be commercially available or under development) like aqueous-based reagents.

Establishing diversified sustainable supply chains of raw materials that are independent of volatile market situations will promote the security of medicines as finished products by the European healthcare industry and contribute to the health of European citizens by safeguarding the continuous availability of drugs for patients. The new chemical technologies developed will provide access to newly discovered fine chemicals and pharma building blocks. This will allow industries to become independent of fossil-based raw materials like crude oil and strengthen the European science and technology community.

The harmonisation of environmental sustainability assessment methodologies across the whole healthcare sector will influence European environmental regulations to make life cycle assessments (LCA) comparable between different pharmaceutical manufacturing processes and will contribute to establishing a novel European LCA guideline, aligned with the EU Product Environmental Footprint[2] methodology and its underlying relevant methods and standards.

[1] Environmental considerations in the selection of medical staplers: A comparative life cycle assessment, Journal of Cleaner Production, 371, 2022, 133490.
[2] https://eplca.jrc.ec.europa.eu/permalink/PEF_method.pdf

The project will provide a recognised contribution from the life science sector to the Green Deal[3] and Chemicals Strategy for Sustainability[4] of the European Union, in line with the Pharmaceutical Strategy for Europe[5].

Expected outcomes

We expect all of the following outcomes to be generated from the topic.

1. Generation of novel, process-intensified manufacturing methods and unit operations according to safe and sustainable by design (SSbD) principles with the following goals.

    a. Reducing solvent volumes in chemical synthesis and cleaning operations: Large volumes of pure and high-quality organic solvents are required for pharmaceutical manufacturing without ever being reused or recovered. The goal is to identify ways to either eliminate solvents, by increasing the usage of water-based reactions; reuse solvents; or more preferably avoid entirely the use of high solvent volumes. Innovative methods (e.g. surface functionalisation) of cleaning and rinsing techniques (equipment, medical devices) need to be developed to minimise solvent waste.

    b. Replacement of substances of concern:

        i. by either replacing reagents with less toxic chemicals, e.g. replacements of chlorinated solvents, toxic reagents, heavy metal based homogeneous catalysts;

        ii. by identifying alternative routes to target the chemical transformation, e.g. through catalytic or biocatalytic rather than stoichiometric chemical transformations, or by reducing the overall number of steps (e.g. through cascade reactions) with a significant impact on the use of solvents and chemicals.

    c. Reducing total water volumes in fermentation processes (both upstream and downstream) by innovative fermentation designs, e.g. continuous manufacturing, perfusion technology and reusable downstream processing aids, or preferably by reducing or recycling the purified water (PW), and particularly high quality water (e.g. sterile water for injection (WFI)) volumes.

    d. New fermentation/cultivation and purification technologies (e.g. alternatives to chromatography or innovative chromatography technologies, buffers and resins) with reduced water and energy demands.

    e. Reducing energy consumption in chemical or biotechnological processes: Heating, cooling and sterilisation / cleaning in place (CIP/SIP) operations are energy intensive. Use of alternative chemical transformation steps or sterilisation techniques should help to reduce energy consumption.

    f. Harvesting new sources of raw materials other than fossil sources to have reliable access to readily-available starting materials, solvents, reagents, homogeneous catalysts (where possible transition metal based or, if necessary, rare earth metal based) or biocatalysts (enzymes for catalytic chemical transformations).

[3] https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en
[4] https://environment.ec.europa.eu/strategy/chemicals-strategy/implementation_en
[5] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020DC0761

g. Changing biomanufacturing[6]: Many biotechnological manufacturing processes rely on single-use equipment, consumables and materials, and this contributes to an increase in solid waste generation, especially plastics. Novel single-use materials will be developed from renewable sources with the possibility of recovering valuable materials like transition metals/rare earth metals from electronic components of single-use equipment (single-use reactors, electrodes, probes etc.) or using single-use equipment manufactured from renewable resources.

2. According to the World Economic Forum 2022 report, the pharmaceutical industry is fuelling the climate crisis where the sector is responsible for 4.4% of global emissions and its CO_2 footprint is forecast to triple by 2050[7]. Reducing the generation of greenhouse gases (mainly CO_2, methane, nitrous oxide) is a key element to preventing climate change. Any attempt to improve the efficiency and environmental compatibility of a manufacturing process under development is expected to reduce the generation of GHGs everywhere on the planet. A thorough assessment of the origins and the life cycles of all chemicals, reagents, solvents and API (active pharmaceutical ingredient) drug substances procured must be performed to have a complete cradle-to-gate analysis of the GHG generation to be measured as GHG footprint per mass/dose/treatment. All changes in manufacturing processes should include considerations of the economic impacts. This includes the development of thresholds for the recovery and reuse of solvents.

3. All aspects of process designs should be quantified in standardised assessment systems comprising as many influence factors as possible to describe the full environmental impact of a single drug product on everybody's environment. Artificial intelligence (AI) / machine learning (ML) driven technology should help to sharpen the full picture of the environmental impacts from material supplies via manufacturing to the consumer and waste (= cradle-to-gate analysis). A publicly accessible digital toolbox will be developed that guides development chemists, biotechnologists and engineers to create the best possible manufacturing processes that produce safe and high-quality products with the minimum environmental impact possible.

4. The harmonisation of assessment systems[8] across the healthcare industry is expected to be incorporated into European environmental guidelines, and standards aligned with existing standards outside the scope of the EC.

Scope

Many programmes launched on green chemistry and green pharmaceuticals (e.g. Innovative Medicines Initiative [IMI] projects like CHEM21 and iCONSENSUS, or HORIZON-HLTH-2021-IND-07-01 projects) aim to demonstrate the technical feasibility of applying new methods to improve the overall efficiency and robustness of single manufacturing steps and how to assess their impact on the environment.

The scope of this topic is as follows.

- To transfer approaches from green chemistry and technology into biomanufacturing by developing new types of upstream and downstream processing methods with increased efficiency, more balanced energy consumption and less waste (stainless steel vs. single-use equipment), continuous manufacturing (perfusion cell cultures vs. fed-batch), and the production of enzymes as process reagents in the manufacture of pharmaceutical products.

[6] The term "biomanufacturing" describes all manufacturing methods that utilize procaryotic or eucaryotic cell systems to produce biomolecules for use in medicines (e.g. therapeutic proteins, monoclonal antibodies (mABs), mRNA for vaccines) or chemical synthesis (e.g. enzymes).
[7] https://www.weforum.org/agenda/2022/11/pharmaceutical-industry-reduce-climate-impact
[8] Assessment System means a set of measures that collects and analyses data of raw materials, consumables, equipment performance, and unit operations to evaluate and improve the performance of inputs, the unit, and its output.

- To apply innovative technology to the chemical synthesis of e.g. small molecules, oligonucleotides, peptides and vaccines, by removal of hazardous chemicals, and streamline manufacturing processes and energy consumption, mainly by introducing new production and analytical technologies using “greener” solvents, smaller solvent volumes (e.g. mechanochemistry, alternatives to chromatography), continuous manufacturing processes (e.g. flow-chemistry) and emphasising catalysis and enzymatic chemistry. More sustainable sterilisation processes as alternative to ethylene oxide sterilisation for devices.

- To identify, characterise and test novel replacement materials for single-use equipment and process aids (tubing, bags, PVCs (polyvinyl chlorides)) based on materials from renewable sources, e.g. BioPET (biorenewable polyethylene therephthalate).

- To create new life cycle assessments (LCA) of drug substances and drug products of all (including new) modalities[9] to gain a holistic view of the end-to-end environmental impact of all materials, energies, chemicals and wastes involved in the production of medicines, with the ultimate goal of achieving comparability of diverse manufacturing processes, technologies and products, e.g. chemical entities (tablets / liquid formulations) or biologics (lyophilised / liquid formulations).

- To promote diversified value/supply chains resulting in a shift away from dependencies on specific suppliers and ingredients, thereby promoting the security and resilience of the European pharmaceutical and healthcare industry and the health of European citizens.

- To harmonise and standardise the definitions, manufacturing ontologies, methodologies and frameworks for environmental impact assessment (e.g. LCA standards) of healthcare, including pharmaceutical products, across the European healthcare sector, and align with industries outside the EU (north America, Asia, UK etc.).

- To evaluate the applicability and relevance of the proposed solutions, existing impact assessments (e. g. life cycle assessments, based on existing industry standards, e.g. the standard developed by the Sustainable Markets Initiative, SMI) should be performed to show superiority in comparison to existing approaches.

Previous and current projects (cf. HORIZON-HLTH-2021-IND-07-01 projects IMPACTIVE, ENVIROMED, ETERNAL, SusPHARMA and TransPharm) have a strong focus on the environmental impact of current and new manufacturing technologies at low technology readiness level (TRL) using life cycle assessments. In this project, the industrialisation of new technology is pursued more intensively and on a larger scale at higher TRL by all partners. In this project, the standardisation of environmental impact assessment methodologies (e.g. LCA) of industrial processes is prioritised rather than the individual assessment of new technologies.

Continuous alignment and exchange with the relevant projects from the existing Horizon Europe and IMI programmes will avoid duplication of the work and allow for the harmonisation of scientific efforts.

Resources and learnings from previous and ongoing initiatives (e.g. projects funded under IMI1 / IMI2[10] or other Horizon 2020, Horizon Europe, NextGenEU and EU4Health projects) should also be taken into consideration.

[9] The term “modality” includes biologically active macromolecules like proteins, oligopeptides, oligonucleotides/mRNA, vaccines, and protein conjugates.
[10] Findings from the IMI-funded projects CHEM21 and iCONSENSUS may be relevant. The CHEM21 project aimed to identify reactions and methodologies that addressed bottlenecks in the sustainability of processes applied to the synthesis of active pharmaceutical ingredients (APIs). The iCONSENSUS project aims to develop innovative analytical, hardware, software and high-throughput tools for the development, monitoring and control of mammalian cell cultivation processes for the production of biopharmaceuticals.

Current projects like IMI project PREMIER[11] demonstrate the impact of drug substances, by bioaccumulation, in living organisms and mobility across the environment. In contrast, the aim of this project is to avoid the accumulation or distribution of any substances of concern in nature and therefore identify new transformations that can replace stoichiometric or catalytic use of toxic reagents or catalysts, respectively.

Most fine chemicals originate from fossil sources. Creative utilisation of new sources is the key to directing our future manufacturing efforts into a more sustainable production of second-generation fine chemicals and drugs. Developing new skills and technologies by exploring renewable sources for the bulk production of chemical starting materials of high quality based on European research networks promotes and facilitates Europe's independence from raw material sources outside Europe and diversifies global supply chains. This will make sensitive supply chains more stable and guarantee reliable patient care in Europe.

The compilation of life cycle assessment data is a time-consuming and cost intensive process, requiring the collection of a large amount of data on raw materials, consumables, transport, manufacturing utilities, devices and other materials needed during the use phase and waste treatment of pharmaceutical products. Therefore, LCAs are created when the asset has already reached a mature development state. Early involvement of product environmental data can help guide development scientists in a more sustainable and overall impactful direction of manufacturing processes and technologies. While ongoing projects such as TransPharm[12] focus on developing new impact assessment methodologies for assessing the sustainability of pharmaceuticals, the project in this call will be complementary by applying harmonised standards for LCA. A harmonised set of standard data will be applied in close collaboration with SMI (Sustainable Markets Initiative) in this project based on a common set of product category rules (PCR), which will be fed into a shared database and digital planning tool that enables a non-expert user to investigate the environmental impact of new process designs, or later process or product changes. EU PEF / PEFCR (= product environmental footprint / product environmental footprint category rules) will be a key reference and over-arching starting point for a medicine-specific Product Environmental Footprint standard.

This project will therefore focus on the standardisation and harmonisation of assessing and scoring the environmental performance of systems across industry: healthcare and API manufacturing by chemical and biotech companies. They have developed a strong commitment to sustainability by design approaches over the past years with individually developed life cycle assessment methodologies to evaluate the environmental impact of their respective process developments and improvements. All methodologies lack a common framework of metrics and quantitative sets of descriptors to allow comparability of identical unit operations with different assessment systems.

The Chemicals Strategy for Sustainability has as its objective the transition towards safer and more sustainable chemicals in line with the SSbD principles. It will require that industry minimises, substitutes as far as possible, and phases out the most harmful chemicals in healthcare products whilst at the same time ensuring the sustainability / availability, safety, quality and efficacy of these products.

The early involvement of European regulatory authorities, both related to environmental footprinting requirements and from a medicine manufacturing perspective, are essential for the harmonisation of standards with existing European directives.

Besides this topic, another topic in this IHI call entitled "Safe & sustainable by design (SSbD) packaging and single use device solutions for healthcare products" will cover the reduction of waste, the recyclability and circularity as well as renewable feedstock of packaging materials. The impact of innovative packaging and device materials on the life cycle assessment (LCA) of the healthcare products will be investigated in this SSbD project. In order to jointly develop new strategies to ensure a greener healthcare industry along the whole value chain, and to avoid overlaps, a close collaboration between the two topics is essential and

[11] https://imi-premier.eu/

[12] https://transforming-pharma.eu/

should be reflected by providing dedicated resources in both projects to align on common LCA methodologies and LCA data.

Why the expected outcomes can only be achieved by an IHI project

Public partners/ small and medium-sized enterprises (SMEs): European science and technology is extremely powerful at collaborating on very basic research in order to create new manufacturing technologies and identifying alternatives to substances of concern (reagents/chemicals) used for manufacturing or as components of materials with direct contact to drug substances (e.g. primary packaging, process aids etc). The development of innovative and truly sustainable manufacturing technology and chemistry requires a highly skilled and modern academic research and innovation network that comprises university research groups, publicly funded research institutes and SMEs. The transformation of industrial manufacturing processes can only start with new knowledge developed and learnings shared from within independent research laboratories in science, engineering and novel therapeutic technologies. The wide scientific and industrial network of the partners in this consortium should serve as a starting point for an exchange with external partners in order to be able to implement the innovations more efficiently.

SMEs with unique platform technologies will feed new aspects into well-established material supply chains and manufacturing.

A project management office will provide administrative support to run the project.

Fine chemical and API manufacturers are the link between pharmaceutical or biotechnological industries and raw material suppliers. They play a key role in the overall life cycle of drug substance manufacturing as providers of chemical building blocks, bulk reagents, solvents and process materials.

Industrial partners will transfer research outcomes into industrial manufacturing practice and demonstrate the scalability of processes and validate the usability of new materials. Industry partners will assess any new ideas for their transferability into a commercial and scalable process to maintain the quality and safety of products and guarantee the safety and efficiency of a novel manufacturing process.

All partners, in combination with regulators, will eventually establish a cross-sectoral, harmonised standard life cycle assessment tool to quantify the environmental impact of different manufacturing routes in development that allows decisions to be made based on data rather than the experience of scientists. This tool should have the capacity to quantitatively support the selection of the most efficient and environmentally benign process by using real world data and innovative digital capabilities such as AI and ML.

Pre-identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI project is composed of the following pharmaceutical and medical technology industry partners:

- AstraZeneca
- Abbvie
- Boehringer Ingelheim
- GSK
- Janssen
- Medtronic
- Merck KGgA
- Novo Nordisk
- Olon
- Pfizer
- Sanofi (Lead)

- Servier
- SwiftPharma

In the spirit of partnership, and to reflect how IHI two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for the second stage, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader.

Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities with regard to such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

The maximum financial contribution from IHI is up to EUR 20 550 000.

The indicative in-kind and financial contribution from industry partners is EUR 20 550 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in kind contributions to operational activities from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).

Indicative duration of the action

The indicative duration of the action is 60-72 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage and the predefined industry consortium may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium

The industry consortium expects to contribute to the IHI project by providing the following expertise and assets:

- Expertise in the development of drug substance and product manufacturing processes, aspects of environmental and occupational safety, cost efficiency, procurement of materials, energies and manufacturing equipment (e.g. supply chains, transportation, energy supply).
- Manufacturing equipment to scale up innovative technologies into the pilot plant scale and run test batches.
- Chemistry, manufacturing and controls (CMC) expertise in the development of new chemical entities or new modalities in terms of quality, patient safety, patient drug delivery systems and economy.
- Provide specifications on product categories and product data to feed the harmonised LCA methodology.
- Provide user requirements, delivery of manufacturing data to generate and feed the LCA tool.

- Provide user requirements to lead the development of new planning tools for safe and sustainable by design (SSbD) tools.

- The overall split of efforts should be 70%-80% investigation of new technologies, and 20%-30% creation of new standards/LCA tools in this project.

- Collaboration with other initiatives, e.g. SMI (Sustainable Markets Initiative), the ACS GCI Pharmaceutical Round Table, the British Standards Institute (BSI) and PEG (Pharmaceutical Environment Group) to harmonise efforts to define new standards of PCR (product category rules) and LCA.

Applicant consortium

The first stage applicant consortium is expected, in the submitted short proposal, to address the entire scope and deliver on the expected outcomes of the topic, taking into account the expected contribution from the pre-identified industry consortium.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium.

A project management office is expected to be member of the applicant consortium to provide the administrative support to run the project.

Applicants should clearly outline their approach for data capture, storage and sharing within the consortium as well as sharing results through peer-reviewed publications or other mechanisms. They must ensure that the relevant results and data repositories will be sustainable after the end of the project and made public.

Applicant consortia shall in addition provide the following expertise or resources.

Grant administration

- To provide financial administration, submission of deliverables, periodic reports etc.

Project management

- To coordinate internal communication and meetings, general oversight and management of communication, exploitation and dissemination activities, risk management.

- To provide and maintain an IT infrastructure, to develop and implement an efficient data governance and management strategy of the joint consortium according to adequate standards and deliver the “data management plan”.

- To coordinate networking, joint activities and synergies with other European initiatives, or other relevant groups (e.g. Horizon Europe and IHI projects).

- To develop a strategy for the exploitation and sustainability of project results and outcomes and deliver the “exploitation and sustainability plan”.

Interactions with regulatory authorities, health technology assessment (HTA) bodies, payers, policy makers, and advocacy groups

- To contribute to the regulatory landscape for life cycle assessment standards in the EU and in other non-EU European countries.
- In conjunction with industry, to discuss with regulatory authorities, standards bodies, and advocacy groups the acceptability and implementation of the LCA metrics in the EU and harmonisation with efforts in other non-EU European countries and the US.
- To prepare relevant documents regarding the approach used and the results generated by the project (e.g. briefing books, European Medicines Agency [EMA] guidance documents).

Technology

- Continuous manufacturing technology (flow chemistry, perfusion cell culture) in combination with online monitoring and in-process control.
- Innovative technology in manufacturing new chemical entities (NCE):
  - demonstrated expertise in pharmaceutically relevant chemical chemistry;
  - compulsory expertise: chemo catalysis and biocatalysis;
  - optional expertise: photochemistry, mechanochemistry, cell-based chemical transformations (oxidations, functionalisations).
- Innovative technology in manufacturing new biological entities (NBE):
  - new fermentation/cultivation technology with low volumes/low energy;
  - demonstrated expertise in pharmaceutically relevant expression systems;
  - innovative chromatography technologies, alternative purification technologies or other purification technologies replacing chromatography;
  - low energy utility preparation (e.g. WFI, steam);
  - ontologies in biomanufacturing.
- Innovative technology in manufacturing new medical devices (MD):
  - cleaning technology avoiding the use of solvents and detergents;
  - sustainable sterilisation processes (e.g. irradiation, supercritical CO_2);
  - analytical methods to track chemical residues in medical devices;
  - checking the safety of new cleaning and/or sterilisation processes according to ISO10993 requirements;
  - cleaning & sterilisation process design based on SSbD framework principles.
- Innovative chromatography.

- Low energy, low solvent volume processes including reactions in/on water and recycling technologies.
- Utilisation and supply of raw materials, fine chemicals, consumables and solvents from renewable sources.
- Reuse technology of organic and aqueous solvents and catalysts to address waste reduction.
- Replacement of substances of concern to avoid regrettable substitutions.
- Expertise in conducting life cycle assessments of pharmaceutical products.
- Knowledge about existing LCA standards, tools and data for chemical and (bio)pharmaceutical products.
- AI/ML supported process design based on SSbD principles.
- Network with healthcare providers and regulatory stakeholders.

At the second stage, the consortium selected at the first stage and the pre-identified industry consortium will form the full consortium. The full consortium will develop in partnership the full proposal, including the overall structure of the work plan and the work packages, based upon the selected short proposal at the first stage.

Dissemination and exploitation obligations

The specific obligations described in the conditions of the calls and call management rules under “Specific conditions on availability, accessibility and affordability” do not apply.